PTO 12-1462

CC=CH
DATE=19850415
KIND=A5
PN=648754

PHARMACEUTICAL SLOW-RELEASE TABLET
[PHARMAZEUTISCHE RETARD-TABLETTE]

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UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. JANUARY 2012
TRANSLATED BY: SCHREIBER TRANSLATIONS, INC.

PUBLICATION COUNTRY	(10):	CH
DOCUMENT NUMBER	(11):	648754
DOCUMENT KIND	(12):	A5
PUBLICATION DATE	(45):	19850415
APPLICATION NUMBER	(21):	7514/79
APPLICATION DATE	(22):	19790816
INTERNATIONAL CLASSIFICATION	(51):	A61K 9/44
PRIOR ART DOCUMENTS	(56):	N/A
PRIORITY COUNTRY	(33):	N/A
PRIORITY NUMBER	(31):	N/A
PRIORITY DATE	(32):	N/A
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DESIGNATED CONTRACTING STATES	(81):	N/A

TITLE (54): PHARMACEUTICAL SLOW-RELEASE TABLET

FOREIGN TITLE [54A]: PHARMAZEUTISCHE RETARD-TABLETTE

PATENT CLAIMS

1. A pharmaceutical slow-release tablet consisting of a pellet in the form of a small rod containing a slow-release tablet composition on a matrix base and one or more active ingredients distributed homogeneously or in longitudinal layers, that has one or more relatively deep scored grooves on one side or on the two opposite sides in the transverse direction and perpendicular to the smallest diameter.

2. The pharmaceutical slow-release tablet pursuant to Claim 1, characterized in that the depth of the dividing grooves on one side, or the total depth of the dividing grooves on the two opposite sides is 1/3 to 2/3, preferably 2/5 to 1/2 of the smallest diameter of the small rod.

The object of the invention is a divisible pharmaceutical slow-release tablet in the form of a small rod.

Pharmaceutical peroral dosage forms with delayed drug release, so called slow-release forms, to maintain the most constant and long-lasting drug concentration in the circulatory system, have already long been known, especially in the form of coated tablets and capsules. Ordinary tablets with deep dividing grooves are also known per se, and accordingly also certain advantages of the deep dividing grooves, namely greater ease of

breaking and therefore more precisely dosed pieces. In this regard, reference may be made to the following patents: US 3 883 647, US D 201 497, US D 202 467, and DE-AS 1 200 790. As yet there are no slow-release tablets that can be broken into predetermined uniform parts with no significant loss of the slow-release activity, as is the case for ordinary tablets, although there is undoubtedly a need for this.

The pharmaceutical slow-release tablet pursuant to the invention is characterized in that it consists of a pellet in the form of a small rod that contains a slow-release tablet composition on a matrix base and one or more active ingredients distributed homogeneously or in layers, that has one or more relatively deep scored grooves on one side or on both sides in the transverse direction and perpendicular to the smallest diameter.

The depth of the dividing grooves on one side, or the total depth of the dividing grooves on the two opposite sides is 1/3 to 1/2, preferably 2/5 to 1/2 of the smallest diameter of the small rod. The side surfaces of the dividing grooves are preferably convex.

The tablet can be biplanar or convex on one or both sides and provided with opposed or staggered dividing grooves, and can accordingly be broken up into two or more predetermined identical or unequal parts. This permits a more individualized

and more precise dosage of the drug depending on the clinical picture and on the patient (weight of adults, children, etc.).

The essence of the invention consists of being able to keep the surface of the break as small as possible by the special forming of the present tablet (small rod-like shape with relatively deep dividing grooves), so that the slow-release effect is changed only slightly and the spread of the weights of the fragments is substantially reduced. Surprisingly, it was also found that the impairment of the slow-release effect for the fragments is smaller than would actually have to be expected based on the enlarged total surface area based on the irregularly structured and porous break surfaces. In addition to the major advantages of easy divisibility and only slightly modified slow-release effect of the broken halves compared to the whole tablet, the slow-release tablets pursuant to the invention also have the following advantages: they can easily be labeled by embossing or imprinting, actually on both sides, for example manufacturer's name on one side and code designation of the drug on the other; they are easily swallowed either whole or as broken-off fragments, considerably more easily than round tablets or pieces of them. Multilayered tablets with different active ingredients or different drug releases can also be produced, and given layers can be arranged so that they show no breakage points when broken.

The surfaces of the breaks can be made even smaller by additional widening of the dividing grooves, but this makes the tablet very fragile, quite aside from the production problems that this causes.

The customary auxiliaries compatible with the active ingredients used can be used to make the slow-release tablets pursuant to the invention. Because the tablets are easily broken and because of the tendency toward capping of the tablets, it turns out that firmly cohesive tablet compositions are preferred.

The matrix material can consist of an inherently inert and indigestible mixture, for example of plastics such as PVC, acrylates, and methacrylates. However, it can also be a material that is subject to progressive softening (for example, hydrophilic gel formers) or to erosion in the gastrointestinal passage (for example lipids mixed with inert carriers or digestible di- and triglycerides). Also, the use of intrinsically non-retarding fillers or carriers such as bentonite, talc, di- and tricalcium phosphate, lactose, silica, cellulose, and the like, at the same time as the retarding materials, may be necessary or beneficial.

In detail, the following can be used as retarding materials:

a) Essentially water-insoluble:

Lipids: Fatty alcohols such as cetyl alcohol, stearyl alcohol, cetostearyl alcohol, glycerides, for example glycerol monostearate, hydrogenated castor oil, mixtures of mono-, di-, and triglycerides from vegetable oils; waxes, for example beeswax, carnauba wax; paraffins, for example paraffin, petroleum wax; fatty acids, for example stearic acid, cellulose derivatives, for example ethylcellulose, acetylcellulose, polyvinyl compounds, for example PVC, polyvinyl acetate, and copolymers with crotonic acid. Polyethylene. Vinyl chloride-vinyl acetate copolymers. Polymers and copolymers of acrylates and methacrylates, for example copolymers of ethyl acrylate and methyl methacrylate.

b) Water-soluble or swellable with water:

Cellulose derivatives, for example methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, Na carboxymethylcellulose (preferably higher-viscosity compounds). Polyacrylic acid (and salts). Natural (anionic) gums: for example xanthan gum, guar gum, tragacanth, alginic acid and salts.

Active ingredients that are not particularly soluble in the neutral intestinal environment but are better soluble in the acidic pH of the stomach, that have functional carboxyl group

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(dissolve in the neutral range), for example shellac, cellulose acetate-phthalate, hydroxypropylmethylcellulose phthalate, half-esters of maleic anhydride copolymers.

To strengthen the tablets pursuant to the invention even more, the pellets can be provided with a soluble film coating. However, it should not be so thick that it would detract too greatly from the fragility and at the same time control the release of the active ingredient or affect it substantially. The preferred thickness is 20-50 µm. Since many drugs are known to have an unpleasant bitter taste, the film coating also covers up the taste. Suitable film coating materials in particular are methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose (especially the last one), often mixed with talc, wetting agents, pigments (to facilitate application and for labeling); a mixture of polyvinylpyrrolidone and polyvinyl acetate with hydroxypropylmethylcellulose, mixtures of shellac with hydroxypropylmethylcellulose or polyvinyl acetate or its copolymers with polyvinylpyrrolidone, and mixtures of water-soluble cellulose derivatives (such as hydroxypropylmethylcellulose) and water-insoluble ethylcellulose. Depending on the solubility of the components, these coatings are applied in aqueous solution or organic solution (mixtures with shellac or ethylcellulose). The following materials can also be used: Mixtures of inherently water-insoluble arylates

[*sic*] (for example ethyl acrylate-methyl methacrylate copolymer), which are used in aqueous dispersion, with water-soluble components, for example lactose, polyvinylpyrrolidone, polyethylene glycol, or hydroxypropylmethylcellulose.

The tablet compositions can be produced by mixing the solid particles (active ingredient and any filler) with retarding agents, or by mixing precoated drug particles with ordinary tablet auxiliaries. The coatings can be applied in fluidized beds, in coating vessels, in high-speed mixers, or using the microencapsulation method.

The pellets can be produced with well-known tableting machines for the manufacture of rod-shaped pellets or multilayered tablets.

Other objectives and benefits of the invention will be found in the following description in combination with the drawing that describes the various forms of embodiment.

In each of Figures 1 to 3, a is a side view, b is a top view, and c is a breaking point of a tablet according to the invention.

Figure 1 shows a tablet with a dividing groove on one side, wherein the layer S1, as described above, can have a composition different from that of layer S2. When the tablet is divided, the layer S1 remains without broken parts. In the case of a combination preparation for example, the slow-release ingredient

is located in layer S1 and the non-retarded ingredient is in layer S2. In the case of a tablet with only one (retarded) active ingredient, the layer S2 can also be a placebo layer. The depth of the groove t, for example, is 1/3 of the height d of the pellet (d = smallest diameter of the pellet).

Figure 2 shows a tablet with two one-sided dividing grooves that can be broken apart correspondingly into 2 unequal or 3 equal parts. The dividing grooves can have the same or different depths.

Figure 3 shows a tablet with 2 pairs of two-sided dividing grooves on opposite sides. This tablet also can be broken apart accordingly into 2 unequal parts or 3 equal parts. With dividing grooves on the two opposite sides, the spread of weights of the fragments is the smallest. The groove depths t of the two-sided opposed grooves can also be different. For example, it is 1/5 of the height d of the pellet for each of the two-sided opposed grooves, or 1/3 to 2/5 of the pellet in total.

Example 1

2.0 kg of metoprolol tartrate, 0.1 kg of colloidal silicon dioxide, 0.2 kg of calcium hydrogen phosphate, and 0.25 kg of microcrystalline cellulose are mixed and granulated in a fluidized bed with 0.6 kg of an aqueous 30% dispersion of 70:30 ethyl acrylate-methyl methacrylate copolymer. The rate of spray injection is 300 ml per minute, and the infeed temperature is

30°C. The mixture is then dried for 20 minutes in the same apparatus with an air feed at 40°C. The granulate is placed in a planetary mixer, 0.8 kg of molten stearyl alcohol heated to 60°C is added, and the mixture is kneaded for 15 minutes. After cooling, the granulate is passed through a screen with a mesh width of 1 mm and mixed in a tumble mixer with 0.05 kg of magnesium stearate, 0.05 kg of colloidal silicon dioxide, and 0.4 kg of hydroxypropylmethylcellulose, viscosity 15,000 cps, for 10 minutes.

This slow-release metoprolol granulate is pressed into tablets with a gross weight of 445 mg each on a carousel tablet press with guided dies with the following dimensions: length 17.0 mm, width 8.0 mm. The dies are convex (dome radius 4.8 mm), and a tapered score line (aperture angle 45°-60°) 2.0 mm deep (based on the cap height) is applied to one of the two. The resulting pellets have a total height of 4.6 mm.

The coating is done in a coating vessel 55 cm in diameter equipped with baffles. 5 kg of pellets are sprayed continuously using a two-part nozzle with a varnish solution or suspension according to the formula below.

0.1 kg of hydroxypropylmethylcellulose (viscosity 5 cps) is dissolved in 1.2 kg of demineralized water, 0.005 kg of Polysorbate 80 and 0.05 kg of talc are added with stirring, and 0.1 kg of a 20% homogeneous suspension of titanium dioxide in a

solution of 0.007 kg of hydroxypropylmethylcellulose (5 cps) in 90% ethanol is added. The sprayed-on mixture amounts to 19 mg (dry weight) per pellet. The infeed temperature is 60°C, and the temperature of the pellets in the vessel is kept at about 35°C.

The rate of disintegration of the film-coated tablets is determined by the diameter method (F. Langebucher, H. Rettig, Drug. Dev. Ind. Pharm. 3, 241 [1977]), with a flow rate of 16 ml per minute with synthetic gastric juice (pH 1.2, without enzymes) during the first hour, and then with synthetic intestinal fluid (pH 7.5, without enzymes) at 37°C. The following results are typical for the release of metoprolol tartrate in % of the theoretical content from whole or halved film-coated tablets:

Time:	Whole Tablet:	Halved Tablet
60 Min.	23%	27%
120 Min.	38%	43%
240 Min.	57%	65%
360 Min.	72%	78%

Example 2

Slow-release granulate from metoprolol tartrate is prepared as in Example 1.

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A non-retarded chlorthalidone granulate is also prepared as follows:

0.25 kg of chlorthalidone, 1.75 kg of lactose, and 0.5 kg of cornstarch are mixed and are formed in a planetary mixer into

a plastic composition with 0.3 kg of a paste of 0.1 kg of cornstarch and 0.2 kg of water. The moist composition is driven through a screen with a mesh width of 2 mm, and is dried in a fluidized bed for 20 minutes at 60°C. The granulate forced through a 1 mm mesh screen and dried is mixed with 0.1 kg of talc, 0.01 kg of magnesium stearate, and 0.29 kg of microcrystalline cellulose.

The two granulates are pressed on a carousel tableting machine with guided dies that permits the production of layered tablets. The non-retarded chlorthalidone granulate is fed in first, and then the metoprolol slow-release granulate is fed in from a second filling funnel. For the pressing, 2 dies are used for 2 different dividing notches, with the following dimensions: length 19.0 mm, width 7.0 mm. The dome radius is 4.2 mm. The tapered dividing notches in the pellet have a depth of 1.7 mm (cap depth) on the side of the metoprolol layer and 0.8 mm on the side of the chlorthalidone layer. A tablet 6 mm high is the result.

The metoprolol is released in the way described in Example 1, and the disintegration time of the non-retarded chlorthalidone layer is 2-3 minutes (disintegration test apparatus according to USP, synthetic gastric juice at 37°C).

Fig. 1a

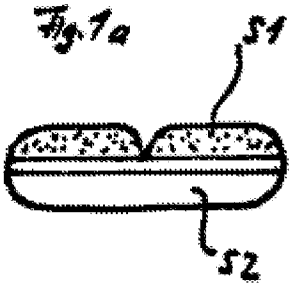

Fig. 2a

Fig. 1/2 a

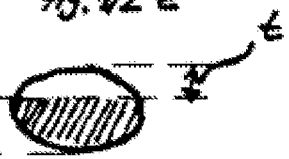

Fig. 1b

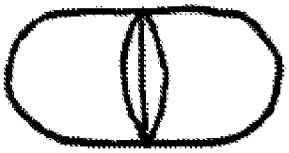

Fig. 2b

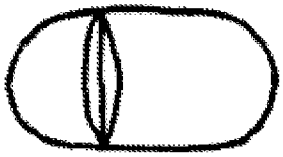

Fig. 3a

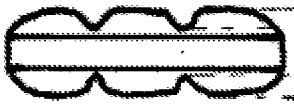

Fig 3c

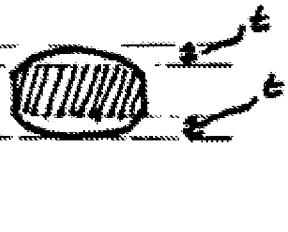

Fig. 3b